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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,599	GODDARD ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-8,28,35-37 and 43-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8,28,35-37 and 43-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 7/26/04, claims 5, 6, 8, 28, 35, 36, 49 have been amended, and claims 9-27, 29-34, 38-42 cancelled. Claims 5-8, 28, 35-37, 43-57 are now pending and under examination.

Applicants' arguments filed 7/26/04 have been considered and found persuasive in part. The previously imposed §102 rejections are withdrawn.

✧

35 U.S.C., §101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 49-52 are rejected under 35 USC §101 because the claimed invention is not supported by a well established utility.

Claim 49 recites that apoptosis can be "prevented", and that cells can be "preserved". Claim 51 recites that organs can be "preserved". However, there is no evidence that this is the case, whether the claimed compounds are used, or prior art compounds are used. "Prevention" of apoptosis implies that not a single cell will undergo apoptosis. For example, if one had a culture of e.g., 10^9 cells, and just <u>one</u> of those 10^9 cells underwent apoptosis (in spite of being contacted with the claimed compound), this would actually constitute evidence that prevention had not been achieved. As for preservation of cells,

there is no evidence that any compound exists which can preserve 100% of cells for an indefinite time period. It may be the case that there exist "immortal" cell lines which can persist indefinitely. But in considering only those cell lines in which apoptosis occurs in the absence of apoptosis-inhibiting agents, there is no evidence of record to indicate that addition of an apoptosis-inhibiting agent will stop 100% of cells from undergoing apoptosis for even a short period of time, to say nothing of indefinitely. As for "preserving an organ", there is no evidence of record that an agent exists which is effective to preserve organ function indefinitely.

With respect to this ground of rejection, it is suggested that the claims be amended to recite that apoptosis of the cultured cells is inhibited, rather than prevented. (However, such a claim may be susceptible to an enablement rejection, since it is not clear what cells other than fibroblasts will be favorably affected by the claimed compounds).

Claims 49-52 are also rejected under 35 USC §112 first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 43-57 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It remains the case that enablement is lacking for the claimed methods. Applicants have argued that the data in table 3 (page 73) shows that compounds 78, 48, 66, 80 inhibit apoptosis. While this may be true, none of compounds 48, 66 or 80 falls within the scope of the claimed genus. Further, the assay was conducted on fibroblasts only. Thus, even if it is true that the compounds of claim 5 can inhibit apoptosis in fibroblasts, it remains to be determined what other cell types will undergo reduced apoptosis in the presence of the compounds, and importantly which other cell types will undergo enhanced apoptosis in the presence of the claimed compounds. As it happens, the skilled artisan who has observed inhibition of apoptosis in one cell line (as a consequence of incubation with compound "X") cannot "predict" what other cell lines will undergo reduced apoptosis in the presence of compound "X". The skilled artisan also cannot predict what other cell types will undergo enhanced apoptosis in the presence of compound "X". For example, Fang X. (*Biochemical Journal* **352 Pt 1** 135-43, 2000) discloses that lysophosphatidic acid inhibits apoptosis in fibroblasts; at the same time, Steiner M. R. (*Annals of the New York Academy of Sciences* **905** 132-41, 2000) discloses that lysophosphatidic acid induces apoptosis in neuronal cells. Thus, if a determination is

made that a given compound will inhibit apoptosis of a given cell type, the skilled artisan cannot predict the cell types in which apoptosis will be inhibited, and the cell types in which apoptosis will be induced. This conclusion is reinforced by the findings of Tsuchiyama Y (*Kidney International* **58** (5) 1941-52, 2000) who discloses that while dexamethasone induces apoptosis in both CD8+ cells and CD4+ cells, Galectin-9 induces apoptosis in CD8+ cells, but fails to induce apoptosis in CD4+ cells.

Furthermore, inhibition of apoptosis is not necessarily going to be "therapeutically effective", or even useful. Consider the following:

- Kanegane Hirokazu (*Pediatric nephrology* (Berlin, Germany) **18** (5) 454-6, 2003) discloses that mutations in the *Fas* gene result in impaired apoptosis (at least *Fas*-mediated apoptosis), and that as a result of this, autoimmune disease and glomerulonephritis occurs. Thus, one would conclude that inhibiting apoptosis will result in autoimmune disease and glomerulonephritis.

- Strasser A. (*Annals of the New York Academy of Sciences* **917**, 541-8, 2000) discloses that Bim is a member of the Bcl-2 family of proteins, and that Bim induces apoptosis. Strasser further discloses that Bim-deficient mice develop autoimmune disease and glomerulonephritis. Thus, one would conclude that inhibiting apoptosis will result in autoimmune disease and glomerulonephritis.

- Van Den Brande, Jan M. H. (*Annals of the New York Academy of Sciences* **973** 166-80, 2002) discloses that Crohn's disease can be treated by inducing T-lymphocyte apoptosis. The skilled artisan would conclude that if Crohn's disease can be treated by inducing apoptosis, then any attempt to inhibit apoptosis would only exacerbate the patient's condition.

- Kacinski B M (*Annals of the New York Academy of Sciences* **941**, 194-9, 2001 discloses that the methods of treating cutaneous T-cell lymphoma that are most successful act by inducing T-cell apoptosis. The skilled artisan would therefor conclude that if cutaneous T-cell lymphoma can be treated by inducing apoptosis, then any attempt to inhibit apoptosis would only exacerbate the patient's condition.

- Tsuchiyama Y (*Kidney International* **58** (5) 1941-52, 2000) discloses that galectin-9 is effective to treat nephritis, and that dexamethasone is also effective in this regard. Both of these agents induced apoptosis of splenic CD8+ cells. The skilled artisan would conclude that if nephritis can be treated by inducing apoptosis, then any attempt to inhibit apoptosis would only exacerbate the patient's condition.

- Li X. C. (*Current Opinion in Immunology* **12** (5) 522-7, 2000) discloses that T cell apoptosis is required for transplantation tolerance. The skilled immunologist would conclude that attempts to inhibit apoptosis would result in transplantation rejection.

- Bednarski Jeffrey J. (*Arthritis and rheumatism* **48** (3) 757-66, 2003) discloses that a compound designated Bz-423 induces apoptosis, and is effective to mitigate autoimmune disease such as glomerulonephritis and arthritis. The skilled immunologist would conclude that attempts to inhibit apoptosis would cause autoimmune disease, or at least exacerbate it.

Thus, as a general proposition, the claimed compounds are just as likely to cause illness as to mitigate it. With regard to claim 54, "dermatological conditions" would include scleroderma, psoriasis, and eczema. It would appear that inhibiting T cell apoptosis is likely to exacerbate such conditions. Then there is the matter of patients stricken with cancer, or persons who are pre-cancerous and predisposed to tumor growth. This would

include skin cancers ("dermatological conditions") as well as other cancers. If the skilled artisan succeeds in inhibiting apoptosis of tumor cells, or pre-cancerous cells, he will only succeed in exacerbating illness, or even causing it.

As for the method of "treating wrinkling" (claim 55), treating hair loss (claim 55), and treating wounds (claim 56), there is no evidence of record that inhibiting apoptosis of fibroblasts (or any other cell types) will be effective in this regard. Further, wounded tissue could potentially encompass any type, e.g.,. epidermal, endothelial, neuronal, intestinal, pancreatic, hepatic, myocardial, etc. There is no evidence that wounds to any of these tissues can be successfully treated.

Claim 47 encompasses treatment of HIV/AIDS. With respect thereto, consider the following:

- Mangos (*Texas Medicine*, **86**, 40, 1990) states the following:

  "In spite of ... [therapy against HIV and opportunistic infections], the universal outcome of HIV infection / AIDS is the death of the patients" (see, e.g., abstract).

- As disclosed in Binquet (*AIDS* **12**, 2313, 1998) a total of 556 patients were treated with HIV protease inhibitors for a period of 230 days, and that despite being treated with with HIV protease inhibitors for more than seven months, 24 of the patients had died. Both this reference, and Mangos, teach that death occurs in spite of administration of HIV protease inhibitors. If death is the result of a treatment, one cannot say that success (in the treatment) is predictable.

- Erickson (*Ann Rev Pharm Toxicol* **36**, 545-71, 1996) discloses that resistance of HIV to drugs is a significant problem, and discusses some of the biochemical mechanisms by which such resistance is conferred.

- Matsushita (*Int J Hematol* **72**, 20-27, 2000) discloses that the benefits of anti-HIV therapy, to the extent that they occur at all, are merely transient when only just one or two agents are used.

While none of Mangos, Binquet, Erickson or Matsushita delves deeply into the subject of apoptosis, the references nonetheless support the proposition that one cannot "predict" efficacy in the treatment of HIV/AIDS on the basis of an apparently effective experiment conducted *in vitro*.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Thus, one cannot extrapolate from inhibition of fibroblast apoptosis to inhibition of other cell types, and further, the claimed compounds are just as likely to exacerbate illness as to treat it. Accordingly, the skilled lipid chemist or immunologist would conclude that "undue experimentation" would be required to use the compounds of claim 5 to treat illness or to "preserve cells" or to "preserve organs".

✧

Claims 5-8, 28, 35-37, 43-57 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention.

- Claim 5 employs the qualifier "about" in reference to ranges. For example, the following are recited: "1 to about 900", "2 to about 10", "0 to about 10", "0 to about 2". However this renders the claims indefinite as to the upper limit on the value of the integer variables.

- Claim 7 is drawn to a composition, and recites a specific compound. However, a composition must have at least two components. A composition that consists of just one compound is not a composition, it is a compound. Accordingly, claim 7 mandates the presence of a second component, without specifying the nature of the second component. It is suggested that claim 7 be amended to recite a second component (perhaps a "carrier").

- Claim 35 is drawn to a method of making a composition, but does not specify any of the components in the final composition. It is noted that step (a) requires preparing a mixture containing a compound of claim 5. But claim 35 would also permit the possibility of removing the compound of claim 5. Does claim 35 require that the final composition contains a compound of claim 5...?

- Claim 43 recites "condition related to apoptosis". What is encompassed by this, or more to the point, which conditions, in applicants opinion, would be excluded? If applicants believe that there are pathological conditions which would be excluded, applicants are requested to provide a few examples.

- Claim 47 recites "apoptosis related problems". What is the nature of such "problems"...? Are they medical in nature and if so, what are they? For example, "problems" could include the inconvenience of making trips to a physician's office; "problems" could include the burden of having to pay for prescription medication. Are such problems included?

- Claim 48 is indefinite as to what is intended by "organ attachment".

- Claim 52 requires the following: (a) that organ preservation be achieved, (b) that the person whose body the organ is present in be administered a compound of claim 5

intravenously, and (c) that the organ in question be earmarked for donation to another human. However, it is not clear how one reconciles these objectives.

✧

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claim 5 is rejected under 35 U.S.C. §103 as being unpatentable over Cherbuliez (*Helv Chimica Acta* **41**, 1163-1168, 1958).

As indicated previously, Cherbuliez discloses (table 3, p. 1167) compound 8. This compound would be encompassed by claim 5 if the substituent variables corresponded as follows:

W = -OH

W = Q (first occurrence)
R = CH_3 and n = 1
X = -O-
X = =O
Z = hydrogen
Y = -O-

Claim 5 does not permit "n" to be 1; claim 5 does permit "n" to be 2, however. The lipid chemist of ordinary skill would have expected substantially identical activity for the two homologs. [*In re Shetty* (**195** USPQ 753) and *In re Hass & Susie* (**60** USPQ 544)].

Thus, the claim is rendered obvious.

✺

DAVID LUKTON
PATENT EXAMINER
GROUP 1600

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.